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Assessment of the Lymph Node Status in Patients Undergoing Liver Resection for Intrahepatic Cholangiocarcinoma: the New Eighth Edition AJCC Staging System

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Abstract

Introduction The role of routine lymphadenectomy for intrahepatic cholangiocarcinoma (ICC) is still controversial. The AJCC eighth edition recommends a minimum of six harvested lymph nodes (HLNs) for adequate nodal staging. We sought to define outcome and risk of death among patients who were staged with ≥6 HLNs versus <6 HLNs.

Materials and Methods Patients undergoing hepatectomy for ICC between 1990 and 2015 at 1 of the 14 major hepatobiliary centers were identified.

Results Among 1154 patients undergoing hepatectomy for ICC, 515 (44.6%) had lymphadenectomy. On final pathology, 200 (17.3%) patients had metastatic lymph node (MLN), while 315 (27.3%) had negative lymph node (NLN). Among NLN patients, HLN was associated with 5-year OS ($p = 0.098$). While HLN did not impact 5-year OS among MLN patients ($p = 0.71$), the number of MLN was associated with 5-year OS ($p = 0.02$). Among the 317 (27.5%) patients staged according the AJCC eighth edition staging system, N1 patients had a 3-fold increased risk of death compared with N0 patients (hazard ratio 3.03; $p < 0.001$).

Gaya Spolverato and Fabio Bagante contributed equally to this work.

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Conclusion Only one fourth of patients undergoing hepatectomy for ICC had adequate nodal staging according to the AJCC eighth edition. While the six HLN cutoff value impacted prognosis of N0 patients, the number of MLN rather than HLN was associated with long-term survival of N1 patients.

Keywords ICC · Surgery · Staging · Nodal status

Introduction

The American Joint Committee on Cancer (AJCC) staging manual is the most common means to stratify cancer patients with regard to prognosis. In the seventh edition AJCC staging manual, a staging system for ICC was introduced for the first time. The newly released eighth edition AJCC T categories have several modifications for ICC staging, including the addition of tumor size to lesion number and vascular invasion [1–7]. AJCC nodal (N) staging has also been a topic of ongoing debate, as the role for routine lymphadenectomy for ICC has been controversial with no standard approach to assessing regional nodal information [2, 8, 9]. In one study using the Surveillance, Epidemiology, and End Results (SEER) cancer registry, Kim et al. reported on 749 patients who underwent surgical resection of ICC between 1988 and 2011 [10]. In this study, Kim et al. assessed the prognostic performance of AJCC/UICC seventh N stage, lymph node ratio (LNR), and log odds (LODDS) among patients with ICC [10]. Interestingly, after curative intent resection of ICC, LODDS and LNR were better predictors of long-term prognosis versus seventh edition AJCC nodal staging. In particular, while LNR performed well among patients who had >3 LNs harvested and examined, LODDS was better at determining prognosis among patients with ≤3 LN examined.

While nodal status appears to be an important factor in determining prognosis of patients with ICC [11, 12], routine lymphadenectomy is not always performed, especially in Western centers [13, 14]. Data on pathological lymph node status are, therefore, often lacking. Importantly, guidelines of the European Association for the Study of the Liver (EASL) on the management of ICC recommend the removal of lymph nodes defined as suspicious according to preoperative imaging [15]. However, the correlation of radiological lymph node status assessment with pathological N status has yet to be determined. As such, the objective of the current study was to correlate the performance of radiological versus pathological assessment of lymph node status among patients with resectable ICC. Moreover, given that the newly released AJCC eighth edition recommends the recovery of at least six lymph nodes for complete pathologic staging, we sought to define the outcome of patients who were "adequately" (≥6 nodes harvested) versus "inadequately" staged (<6 nodes harvested) according to the eighth edition of the AJCC staging manual [16].

Materials and Methods

Patient Demographic and Clinical Data

Patients undergoing liver surgery for histologically confirmed ICC between 1990 and 2015 at one of the following 14 major hepatobiliary centers were identified: Johns Hopkins Hospital, Baltimore, MD; Stanford University, Stanford, CA; University of Virginia, Charlottesville, VA; Emory University, Atlanta, GA; Fundeni Clinical Institute of Digestive Disease, Bucharest, Romania; Curry Cabral Hospital, Lisbon, Portugal; Ospedale San Raffaele, Milan, Italy; Royal Prince Alfred Hospital, University of Sydney, Sydney, Australia; Eastern Hepatobiliary Surgery Hospital, Shanghai, China; Beaujon Hospital, Clichy, France; University of Ottawa, Ottawa, Ontario, Canada; Erasmus University Medical Centre, Rotterdam, Netherlands; Yokohama City University School of Medicine, Yokohama, Japan; and University of Verona, School of Medicine, Verona, Italy. The Institutional Review Board of each institution approved the study. Only patients who underwent curative intent surgery were included, while patients with metastatic disease and patients who underwent an R2 resection were excluded.

Standard patient demographic and clinicopathologic data were collected including age, sex, American Society of Anesthesiologists (ASA) physical status classification, and presence of underlying liver disease, such as cirrhosis, chronic hepatitis B infection, and chronic hepatitis C infection. Serum level of carcinoembryonic antigen (CEA) and cancer antigen (CA) 19-9 was also included. Data regarding treatment details were collected including type of surgery and receipt of adjuvant chemotherapy and radiotherapy. The type of surgery was classified as wedge liver resection, minor resection (removal of ≤2 Couinaud segment), and major resection (removal of ≥3 Couinaud segment) [17]. Resection margin status was recorded and classified as microscopically negative (R0) and microscopically positive (R1). Tumor-specific characteristics including tumor size, number, grade, number of lymph nodes harvested, number of metastatic nodes, presence of vascular invasion (macroscopic and microscopic), perineural invasion, biliary invasion, and direct invasion of contiguous organs were obtained. Lymphadenectomy was performed such that the regional lymph nodes including the nodes in the hepatoduodenal ligament (station 12), the nodes along the common hepatic artery (station 8), and the nodes on the posterior surface of the head of the pancreas (station 13) were harvested, in addition, for left side ICC, also the nodes along the trunk of left gastric artery (station 7). Data on tumor stage were also collected according to both the seventh and the eighth edition AJCC staging system [1, 16]. Nodal status was assessed preoperatively by endoscopic ultrasound echography (EUS), computer tomography (CT) scan, magnetic resonance imaging (MRI), and positron emission tomography (PET) scan; nodes were classified on preoperative imaging as positive, negative, or suspicious. Date of last follow-up and vital status were collected on all patients.

Statistical Analysis

Continuous variables were reported as medians with interquartile ranges (IQRs), while categorical variables were reported as whole numbers and percentages. The endpoint for the survival analysis was overall survival (OS). OS was defined as the time interval between the date of surgery and the date of death. Time was censored at the date of the last follow-up assessment for patients who were still alive at the time of analysis. Survival curves were estimated using the Kaplan-Meier method, and differences between the curves were compared using the log-rank test. Univariate Cox proportional hazard models were used to evaluate associations between variables and OS. The coefficients from the Cox models were reported as hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). A Bayesian model was developed to analyze the prognosis of patients with or without metastatic nodes (N1 versus N0) based on the number of harvested nodes [18]. The results of the Bayesian model were presented as 5-year OS and HR with associated 95% credible intervals (Cr Is). All analyses were performed using the statistical software programs STATA (v. 12.0, StataCorp, College Station, TX), OpenBugs (v.2011), and R CRAN (v. 3.2.2, 2015) with the packages "survival," "Hmisc," and "R2OpenBUGS." A p value <0.10 was considered statistically significant.

Results

Baseline Characteristics of the Study Group

Among 1154 patients who underwent hepatectomy for ICC, most patients were male (n = 638, 55.3%) and younger than 65 years (n = 712, 61.7%; Table 1). Based on the ASA physical status classification, 634 (54.9%) patients were ASA ≤2 and 520 (45.1%) patients were ASA 3 or 4. Preoperatively, a minority of patients (n = 84, 7.3%) underwent neoadjuvant chemotherapy. About two thirds of patients (n = 708, 61.4%) underwent a major hepatectomy, while 157 (13.6%) underwent a wedge resection and 289 (25.0%) a minor hepatectomy. A resection with negative margins (R0) was performed in the majority of patients (n = 992, 87.2%), while 146 (12.8%) patients had R1 resections. Mass forming

Table 1 Baseline characteristics of the study group (n = 1154)

Variables	N (%)
Gender	
Female	516 (44.7%)
Male	638 (55.3%)
Age	
≤65 years	712 (61.7%)
>65 years	442 (38.3%)
ASA score	
≤2	634 (54.9%)
>2	520 (45.1%)
Underlying liver disease	
Cirrhosis	118 (10.2%)
Chronic HBV infection	129 (11.2%)
Chronic HCV infection	15 (1.3%)
None	892 (77.3%)
Neoadjuvant chemotherapy	
No	1065 (92.7%)
Yes	84 (7.3%)
Morphological type	
Mass forming (MF)	941 (87.0%)
Periductal infiltrating (PI)	54 (4.9%)
MF + PI	88 (8.1%)
NA	71
Ca 19-9, median (IQR)	49 U/mL (16.9–204.0)
CEA, median (IQR)	2.4 ng/mL (1.4–4.3)
Type of surgery	
Wedge resection	157 (13.6%)
Minor hepatectomy	289 (25.0%)
Major hepatectomy	708 (61.4%)
Margins	
Negative	992 (87.2%)
Positive	146 (12.8%)
NA	16
Liver capsule involvement	
No	945 (81.9%)
Yes	209 (18.1%)
Tumor size	
≤5 cm	451 (39.1%)
>5 cm	703 (60.9%)
Lesion	
Unifocal	941 (81.5%)
Multifocal	213 (18.5%)
Grade	
Well–moderate	884 (82.5%)
Poor–undifferentiated	188 (17.5%)
NA	82
Major vascular invasion	
Not present	998 (86.5%)
Present	156 (13.5%)
Lymph-vascular invasion	
Not present	771 (69.2%)
Present	356 (30.8%)
NA	27
Perineural invasion	
Not present	805 (78.9%)
Present	215 (21.1%)
NA	134
Preoperative imaging for nodal staging	
Echography	19 (2.2%)
CT	436 (51.3%)
MRI	319 (37.5%)
PET/CT	76 (9.0%)
NA	304
Radiological nodal status	
Negative	608 (52.7%)

Table 1 (continued)

Variables	*N* (%)
Suspicious	118 (10.2%)
Positive	59 (5.1%)
Not reported	369 (32.0%)
Pathological nodal status	
Negative	315 (27.3%)
Metastatic	200 (17.3%)
Not harvested	639 (55.4%)
Lymph nodes harvested[a], median (IQR)	4 (2–8)
Metastatic lymph nodes[b]	
1	110 (55.0%)
2–5	65 (32.5%)
≥6	25 (12.5%)
AJCC eighth edition N status	
N0	117 (10.1%)
N1	200 (17.3%)
NX	837 (72.6%)
AJCC seventh edition T status	
T1	487 (42.2%)
T2a	207 (17.9%)
T2b	123 (10.7%)
T3	195 (16.9%)
T4	142 (12.3%)
AJCC eighth edition T status	
T1a	249 (21.6%)
T1b	270 (23.4%)
T2	402 (34.8%)
T3	167 (14.5%)
T4	66 (5.7%)

NA not available, *IQR* interquartile range

[a] Of 515 patients who underwent lymphadenectomy

[b] Of 200 patients with metastatic nodes;

(n = 941, 87.0%) was the most common morphological subtype of ICC. Overall, 941 (81.5%) patients had a single tumor, while 213 (18.5%) patients had multifocal disease. According to the AJCC seventh edition T staging system, 487 (42.2%) patients were classified as stage T1, 207 (17.9%) as stage T2a, 123 (10.7%) as stage T2b, 195 (19.9%) as stage T3, and 142 (12.3%) as stage T4. Using the AJCC eighth edition T staging system, 249 (21.6%) patients were classified as stage T1a, 270 (23.4%) as T1b, 402 (34.8%) as T2, 167 (14.5%) as T3, and 66 (5.7%) as T4.

Radiological Nodal Status

A total of 785 (68.0%) patients had data on preoperative radiological nodal staging. EUS, CT, MRI, and PET were used to preoperatively assess nodal status in 19 (2.4% of 785), 383 (48.9% of 785), 307 (39.1% of 785), and 76 (9.7% of 785) patients, respectively. Among radiological-staged patients, nodal status was negative (R-NLN) in 608 (77.5% of 785) patients, suspicious (R-SLN) in 118 (15.0% of 785), and metastatic (R-MLN) in 59 (7.5% of 785) patients. Patients with R-NLN had a 5-year OS of 49.7% (IQR, 44.3–54.8) compared with a 5-year OS of 30.1% (IQR, 18.7–42.4) for patients with R-SLN and 25.8% (IQR, 12.5–41.4) for patients with R-MLN ($p < 0.001$; Table 2, Fig. S1). Compared with patients with R-NLN, patients with R-SLN (HR 1.55, 95% CI, 1.15–2.06; p = 0.003) and R-MLN (HR 1.82, 95% CI, 1.27–2.62; p = 0.001) were at higher risk of death (Table 2).

Among 317 (27.5%) patients who had data on both radiological and pathological nodal evaluation, the incidence of NLN was 66.5% (n = 127) among patients initially deemed R-NLN compared with 42.5% (n = 34) among patients who were preoperatively staged R-SLN; in contrast, the incidence of NLN was only 34.8% (n = 16) among patients deemed preoperatively to be R-MLN. The incidence of MLN increased from 33.5% (n = 64) among patients who were R-NLN to 57.5% (n = 46) and 65.2% (n = 30) among patients who were R-SLN or R-MLN, respectively ($p < 0.001$; Table 3). Radiological nodal status was associated with advanced disease (T3/T4 AJCC seventh ed. and eighth ed. stages; both $p \leq 0.003$; Table 3). Of note, the area under the receiver operating characteristic (ROC) curve comparing nodes deemed preoperatively as positive or suspicious versus documented metastatic nodal disease on final pathology was 0.63.

Nodal Status

At the time of hepatectomy, nodes were harvested in 515 (44.6%) patients, while 639 (55.4%) patients did not undergo lymphadenectomy. When lymphadenectomy was performed, the median number of harvested lymph node (HLN) was 4 (IQR, 2–8). Overall, 200 (17.3%) patients had metastatic lymph nodes (MLNs), and 315 (27.3%) patients had no evidence of lymph node metastasis (NLN). Among the 200 (17.3%) patients with MLN, 110 (55.0% of MLN group) patients had 1 MLN, 65 (32.5% of MLN group) 2–5 MLNs, and 25 (12.5% of MLN group) ≥6 MLNs. Among the 315 (27.3%) patients with NLN, 67 (21.3% of NLN group) patients had 1 HLN, 131 (41.6% of NLN group) 2–5 HLNs, and 117 (37.1% of NLN group) ≥6 HLNs. The 5-year OS of patients with NLN was 44.4% (IQR, 36.9–51.6) versus 15.2% (IQR, 8.7–23.4) for patients with MLN (HR 2.42, 95% CI 1.88–3.13; $p < 0.001$; Fig. 1).

To verify the prognostic role of six HLNs as the minimum number recommended by the AJCC eighth edition staging system for an adequate nodal staging, MLN and NLN patients were dichotomized in two groups with a cutoff of six HLNs. Among the 200 (17.3%) patients with MLN, 100 (50.0% of MLN group) patients had ≥6 HLNs with a 5-year OS of 17.9% (IQR, 8.6–29.9) versus a 5-year OS of 12.5% among the 100 (50.0% of MLN group) patients who had <6 HLNs (IQR, 4.7–24.2; p = 0.71; Fig. S2). Patients with MLN had a similar risk of death when stratified by <6 versus ≥6 HLNs (HR 1.07, 95% CI 0.75–1.52, p = 0.72). Among the 315 (27.3%) patients with NLN, 117 (37.1% of NLN group) patients had ≥6 HLNs with a 5-year OS of 54.9% (IQR, 41.6–

Table 2 Comparison of nodal status—Kaplan-Meier analysis and risk of death

	N = 1154	5-Year OS	95% CI	*p* value	HR	95% CI	*p* value
Radiological nodal status				<0.001			
Negative	608 (52.7%)	49.7%	44.3–54.8		–	–	–
Suspicious	118 (10.2%)	30.1%	18.7–42.4		1.55	1.15–2.06	0.003
Positive	59 (5.1%)	25.8%	12.5–41.4		1.82	1.27–2.62	0.001
Not reported	369 (32.0%)	30.7%	25.3–36.2		1.57	1.30–1.90	<0.001
Pathological nodal status				<0.001			
Negative	315 (27.3%)	44.4%	36.9–51.6		–	–	–
Metastatic	200 (17.3%)	15.2%	8.7–23.4		2.42	1.88–3.13	<0.001
Not harvested	639 (55.4%)	44.0%	39.2–48.7		1.18	0.96–1.47	0.11
AJCC eighth edition N stage				<0.001			
N0	117 (10.1%)	54.9%	41.6–66.3		–	–	–
N1	200 (17.3%)	15.2%	8.7–23.4		3.03	2.08–4.42	<0.001
NX	837 (72.6%)	42.9%	38.6–47.1		1.46	1.04–2.07	0.031
Negative nodal status				0.098			
NLN with ≥6 HLNs	117 (37.1%)	54.9%	41.6–66.3		-	-	-
NLN with <6 HLNs	198 (62.9%)	39.4%	30.6–48.1		1.39	0.94–2.07	0.098
Metastatic nodal status				0.72			
MLN with ≥6 HLNs	100 (50.0%)	17.9%	8.6–29.9		–	–	–
MLN with <6 HLNs	100 (50.0%)	12.5%	4.7–24.2		1.07	0.75–1.52	0.72
Radiological nodal status in NHN				<0.001			
Negative	417 (65.3%)	52.3%	46.1–58.2		–	–	–
Suspicious	38 (5.9%)	24.8%	9.3–44.2		1.55	1.15–2.07	0.003
Positive	13 (2.0%)	20.1%	3.3–47.1		1.82	1.27–2.62	0.001
Not reported	171 (26.8%)	32.1%	24.3–40.0		1.58	1.31–1.90	<0.001

OS overall survival, *CI* confidence interval, *HLN* harvested lymph node, *MLN* metastatic lymph node

66.3) compared with a 5-year OS of 39.4% (IQR, 30.6–48.1; $p = 0.098$; Fig. S3) among the 198 (62.9% of NLN group) patients who had <6 HLNs. Interestingly, patients with NLN who had <6 nodes harvested tended to have an increased risk of death compared with patients who had ≥6 HLNs (HR 1.39, 95% CI 0.94–2.07, $p = 0.098$).

Patients Without Nodes Harvested

A total of 639 (55.4%) patients did not undergo lymphadenectomy (Nx); Nx patients had a 5-year OS of 44.0% (IQR, 39.2–48.7) (HR 1.18, 95% CI 0.96–1.47; $p = 0.11$) (Table 2). When pathological Nx patients were stratified according to

Table 3 Association between radiological nodal status, pathological nodal status, AJCC seventh ed., and AJCC eighth ed. T stages

	Radiological modal status			*p* value
	Negative	Suspicious	Positive	
Pathological nodal status[a]				<0.001
Negative	127 (66.5%)	34 (42.5%)	16 (34.8%)	
Positive	64 (33.5%)	46 (57.5%)	30 (65.2%)	
AJCC seventh edition T stages[b]				<0.001
T1/T2a/T2b	471 (77.5%)	74 (62.7%)	31 (52.5%)	
T3/T4	137 (22.5%)	44 (37.3%)	28 (47.5%)	
AJCC eighth edition T stages[b]				0.003
T1a/T1b/T2	406 (66.8%)	70 (59.3%)	27 (45.8%)	
T3/T4	202 (33.2%)	48 (40.7%)	32 (54.2%)	

[a] $n = 317$ patients

[b] $n = 785$ patients

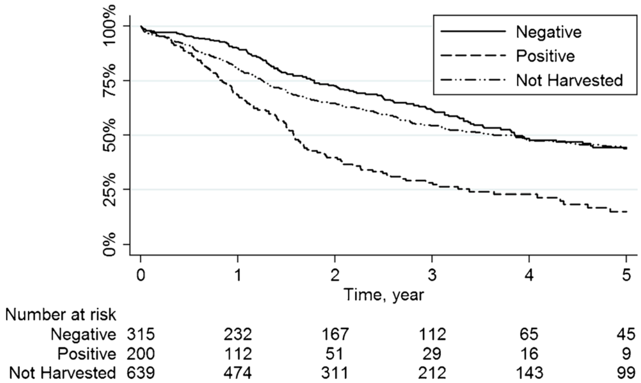

Fig. 1 Kaplan-Meier overall survival curves stratified by pathological nodal status

preoperative radiological nodal status, 417 (65.3%) were in the R-NLN group, 38 (5.9%) in the R-SLN, and 13 (2.0%) in the R-MLN group; 171 (26.8%) did not have any information on radiological node status (R-Nx). Among pathological Nx patients, 5-year OS among patients with R-NLN was 52.3% (IQR, 46.1–58.2) versus 24.8% (IQR, 9.3–44.2) for R-SLN, 20.1% (IQR, 3.3–47.1) for R-MLN and 32.1% (IQR, 24.3–40.0) for R-Nx (Table 2). Compared with patients who had R-NLN, patients with R-SLN (HR 1.55, 95% CI 1.15–2.07), R-MLN (HR 1.82, 95% CI 1.27–2.62), and R-Nx (HR 1.58, 95% CI 1.31–1.90) had an increased hazard of death (all $p \leq 0.003$; Table 2).

AJCC Eighth Nodal Staging

Among the 317 (27.5%) patients with MLN or NLN with ≥6 HLNs—the cutoff recommended by the AJCC eighth edition staging system—117 (36.9% of 317) patients were defined as N0 and 200 (63.1% of 317) as N1. The 5-year OS of N0 patients was 54.9% (IQR, 41.6–66.3; Table 2) versus 15.2% (IQR, 8.7–23.4) for N1 patients ($p < 0.001$; Fig. 2). In turn, N1 patients had an increased hazard of death compared with N0 patients (HR 3.03, 95% CI 2.08–4.42; $p < 0.001$).

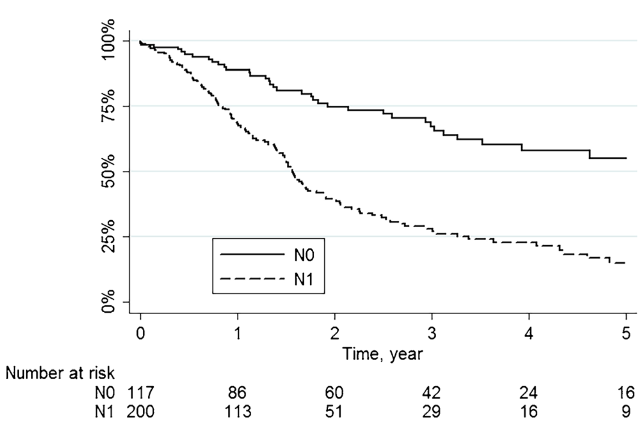

Fig. 2 Kaplan-Meier overall survival curves stratified by AJCC eighth edition nodal stages

To further investigate the effect of the number of HLN on the prognosis of N0 and N1 patients, a Bayesian Weibull model was developed. N1 patients had an increased risk of death (HR 2.42, 95% Cr Int, 1.69–3.38) compared with N0 patients who had one HLN. Of note, when the number of HLN was increased to 3, 6, 8, and 10, the risk of death among N1 patients versus N0 patients increased incrementally to 2.61, 2.89, 3.11, and 3.34, respectively. Specifically, 5-year OS among N0 patients increased with higher numbers of HLN from 38.3% with 1 HLN to 42.7, 49.2, 53.4, and 57.3% with 3, 6, 8, and 10 HLNs, respectively. Conversely, 5-year OS among N1 patients did not varying considerably when HLN increased, ranging from 9.7% with 1 HLN to only 15.5% with 10 HLNs (Table S1).

Discussion

Several studies have investigated a variety of clinicopathological factors and long-term survival, identifying tumor size, tumor number, vascular invasion, and lymph node metastasis as independent predictors of OS and recurrence-free survival (RFS) among patients undergoing surgery for ICC [2, 15, 19, 20]. In particular, the role of lymphadenectomy for ICC has been extensively debated [2, 8–10]. In a recent meta-analysis that evaluated the management of lymph node basin during liver resection for ICC, the authors suggested that surgeons should strongly consider lymph node dissection at the time of surgery although there was insufficient data to support a strong recommendation for routine lymphadenectomy [21]. The newly released eighth edition AJCC staging manual advocates, however, for recovery of at least six lymph nodes during the time of surgery for ICC [16]. Given the large variability in lymphadenectomy among Eastern and Western centers, little data exist regarding the optimal number of lymph nodes to harvest at the time of surgery for ICC. In addition, no study has explicitly sought to evaluate the prognostic relevance of preoperative radiological versus pathological lymph node status. While several studies have evaluated the sensitivity, specificity, and predictive value of ultrasound, CT, MRI, and PET [22–24], no study had assessed the prognostic ability of preoperatively determine N status and long-term outcomes following resection of ICC. The current study was important, therefore, as we determined the prognostic impact of preoperative radiologic nodal status. In addition, we assessed the eighth AJCC edition's recommendation for a minimum recovery of six lymph nodes and its association with long-term outcome among a large multiinstitutional cohort of patients with ICC.

In addition to pathological staging, preoperative radiological lymph node status, as assessed by EUS, CT, MRI, or PET, was correlated with long-term prognosis among patients undergoing resection of ICC (Table 2). Specifically, patients who had metastatic lymph node disease on preoperative imaging had a 5-year OS of only 25.8%, which was almost one half the 5-year OS (49.7%) among patients who had no lymph node disease suspected on preoperative imaging. Interestingly, patients who had nodes deemed as suspicious on preoperative imaging had a comparable 5-year outcome (30.1%) as patients who had metastatic nodes. In fact, patients who had nodes deemed as positive or suspicious on preoperative imaging had an 82 and 55% increased hazard of death long-term compared with patients who had no nodal disease.

Perhaps not surprisingly, pathological nodal status also was associated with prognosis and, in fact, was much more strongly correlated with long-term outcome than preoperative lymph node assessment. Specifically, patients with pathologic N1 disease according to the AJCC eighth edition staging system had almost a 2.5-fold increased risk of death at 5 years compared with N0 patients. The superiority of pathological versus radiological nodal status to predict long-term survival might be expected. While preoperative imaging can often accurately predict "true" nodal status, some inaccuracy and lack of correlation of preoperative imaging with final pathology can occur. Specifically, in the current study, the area under the ROC curve comparing nodes that were "positive" or "suspicious" on preoperative imaging with true nodal disease on final pathology was 0.63. These data suggest that the correlation of preoperative imaging to detect nodal disease was good to fair. Moreover, radiological node status was also correlated with both AJCC seventh and eighth editions' T stages, as patients with advanced T stage disease were more likely to have positive or suspicious nodes on the preoperative imaging (Table 3).

Recently, the AJCC eighth edition proposed a cutoff of six lymph nodes to N stage patients adequately. The impact of number of nodes examined has not been examined among patients undergoing resection of ICC. As such, we investigated the effect of a cutoff of six nodes on long-term outcome. Of note, OS among patients with N0 disease who had ≥6 HLNs was 54.9%, which was markedly better than the 15.2% survival noted among patient with N1 disease. Perhaps of more interest, when assessed using a Bayesian Weibull model, the 5-year OS of N0 patients improved with increasing numbers of HLN, while the 5-year OS of N1 patients did not change with a higher number of HLN (Table S1). In addition, while the 5-year OS of patients with N1 disease who had ≥6 HLNs was no different than patients who had <6 HLNs, the 5-year OS of patients with N0 disease with <6 HLNs was somewhat worse versus N0 patients who had a more thorough lymph node harvest of ≥6 nodes.

The study had several limitations that should be considered when interpreting the results. While one strength of the current report was that it involved multiple centers, the multiinstitutional nature likely led to different radiological imaging techniques. In turn, the sensitivity and specificity of these different techniques in staging the nodal basin may vary [23–25]. The multicenter nature of the study also did not allow for standardization of operative or perioperative approach, especially in terms of performance and extent of lymphadenectomy. Finally, the long duration and the multiinstitutional nature of the study likely caused some heterogeneity in ICC treatment approach. However, given the rarity of ICC, obtaining data from multiple centers increased the sample size and made the data more generalizable.

Conclusion

In conclusion, while pathological nodal status was strongly associated with long-term outcome, only one fourth of patients undergoing liver resection for ICC had adequate nodal staging according to the newly released AJCC eighth edition staging system. Moreover, our results suggested that radiological lymph node staging could be inaccurate in up to 40% of patients and should not be considered a valid alternative to lymphadenectomy. Furthermore, the best ability to discriminate between patients with favorable prognosis and patients with poor prognosis based on the lymph node status was reached when ≥6 lymph nodes were harvested. In other words, the quality of the lymph node staging in terms of hazard of death of metastatic patients compared with non-metastatic patients increased from 1.6 to 1.8 with radiological assessment to 2.4 with pathology assessment; of note, the hazard of death increases to 3-fold when the AJCC eighth ed. staging system recommendations were fulfilled. While the six HLN cutoff value was associated with prognosis among patients staged as N0, the number of HLN was not associated with long-term survival among patients with N1 disease. These data serve to emphasize the important prognostic role of pathological staging of nodal disease among patients undergoing resection of ICC.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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